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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/355,210	07/12/2000	Raffaello Giorgi	515-4167	6135

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/355,210	Giorgi
Examiner	**Art Unit**
David Lukton	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 1, 2001*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) ~~1-15~~ 1-100 is/are pending in the application.

4a) Of the above, claim(s) 4 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) ~~1-3 and 5-15~~ 5-100 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Pursuant to the directives of paper No. 17 (filed 3/18/02), claims 1-3, 5-8, 12-14 have been amended, and claims 16-18 added. Claims 1-18 are pending. Claim 4 remains withdrawn from consideration; claims 1-3, 5-18 are examined in this Office action.

Applicants' arguments filed 3/18/02 have been considered and found not persuasive.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the specification as filed, there was a requirement that when R_1 and R_2 represented benzyl, *neither* of R_3 and R_4 could represent isopropyl. Now, claim 1 mandates that R_3 and R_4 *both* represent isopropyl. This may be just an error, but in any case, it should be corrected.

*

Claims 8-9 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing

subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have asserted (p. 27) that they have subjected "the compounds of the invention" to *in vitro* assays, as described on page 27 (and references cited therein). Applicants have also asserted that "the compounds of the invention" were "active" in the assays. These assertions are left unchallenged at this time. In the cited claims it is asserted that the compounds are effective to treat various diseases. However, there is no evidence that this is the case. Merely because the asserted antagonism may take place *in vivo* does not mean that there exists a single disease or disorder for which benefit will accrue to a patient. The degree of antagonism might not be sufficient to achieve a perceptable effect; moreover, the NK-2 receptor might not be a critical element in any of the recited disorders, i.e., even if the NK-2 receptor could be blocked to the extent of 100% *in vivo*, it does not necessarily mean that the symptoms of any disease will recede. In response, applicants have argued that "it is well known that the diseases... are linked with the activity of NK-2 receptors ... therefore compounds which have an antagonistic activity on these receptors [in vitro] are useful in the treatment of such diseases. However, this is not necessarily true. The fact is that, whether has shown antagonism of a receptor or stimulation of the same, extrapolation from this to treatment of diseases

leads to "unpredictable" results. As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. Consider the following:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH_2 (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) 55 (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to

additional determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) 2 (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4-D-Phe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

Accordingly, merely because NK-2 receptors can be antagonized *in vitro* does not mean that any of the compounds will be useful to treat asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, spasms of the bladder, spasms of the ureter, kidney infections, or colics. It follows that "undue experimentation" would be required to practice the invention of claims 8, 9 and 14.

*

Claims 1-3, 5-15 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 1, last two lines recites:

  "R3 and R4 .... **and** an acceptable salt or enantiomer thereof".

  Here, the conjunction "or" should be used rather than "and", in addition, "or" should be preceded by a semicolon.

- Claim 1 recites that R_9 and R_{10} can form a 4-6-membere hereterocycle "possibly containing" another heteroatom. Here *optionally* would be preferable to "possibly". Simlarly, Claim 1 recites that R_{12} is "possibly protected".

- In claim 2, "phenyl alanine" should be one word, rather than two.

- Claim 2 recites "L is a chemical bond **of** CH2".

  It appears that **or** is intended, rather than "of".

- In claim 2, 12th line from last, the following is recited: "arabinose." Here, a comma, rather than a period should be used.

- In claim 2, 11th line from last, the following is recited: "their N-acetylated derivatives". However, "their" tends to indicate possession, which is not appropriate. In addition, it is not clear what "their" even refers to, since ribose, arabinose, glucose, galactose, fructose do not have amino groups to begin with. It is suggested that the phrase at issue be deleted, and that the following two Markush Group members be added: N-acetylglucosamine and N-acetylgalactosamine.

- In claim 2, 8th line from last, the following is recited: "from2". This should be two words, rather than one.

- In claim 2, 8th line from last, the following is recited: "groups,C_{1-6}". Here, there should be a space between "groups," and "C_{1-6}".

- In claim 2, 6th line from last, there are two right-hand parentheses, and only one left-hand parenthesis. It appears that one of the right-hand parentheses is unmatched.

- In claim 3, the conjunction "and" should precede the last member of the Markush Group.

- Claim 5 ends in two periods; there should be just one.

- Claim 12 recites the following:

  "for a time and under conditions effective to antagonize an NK-2.

  This should instead be the following:

  ...for a time and under conditions effective to antagonize **said** NK-2.

  The same applies in the case of claim 13.

- Claim 9 is not enabled. Setting that aside, however, the term "anxiolytics" should be in the singular.

- Claim 10 is drawn to a method of antagonizing tachykinin. How is this possible, biochemically? That is, how is it possible to antagonize tachykinin, while leaving the tachykinin receptors unaffected? Is there an assay which applicants are aware of, or which can be hypothesized, which could demonstrate this? It is suggested that the claim be limited to antagonizing the receptor only.

- Claim 10 recites "tachykinin peptide receptors". It appears that the term "peptide" within this phrase is superfluous.

- In claim 14, "the patient" lacks antecedent basis.

- Claim 14 suggests that formula (I) *per se* is administered to to patient. However, a formula is more of a mental construct than an actual physical entity. It is suggested that the claim be amended to recite that *a compound of formula (I)* is administered

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 are rejected under 35 U.S.C. §102(b) as being anticipated by Rothe, M. (*Pept., Proc. Eur. Pept. Symp.* 14th, 71-8, 1976).

Rothe discloses (table 1, page 72) the compound fungisporin, which is

cyclo-Phe-Phe-Val-Val

Claim 1 is anticipated for the case of variables R_1 and R_2 representing benzyl, and R_3 and R_4 representing the side chain of valine. Claim 1 has been amended; the requirement that R3 and R4 represent isopropyl may be an error, but as the claims stands, they are anticipated.

*

Claims 1-2 are rejected under 35 U.S.C. §103 as being unpatentable over Kitakabake

(*Peptide Chemistry*, **17**, 7, 1980).

As indicated previously, Kitakabake discloses the following compound:

cyclo-Val-Val-Phe-Phe.

The previous proviso has been eliminated; the requirement that R3 and R4 represent isopropyl may be an error, but as the claims stands, they are anticipated.

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1, 2, 5-9, 15 are rejected under 35 U.S.C. §103 as being unpatentable over Kitakabake (*Peptide Chemistry*, **17**, 7, 1980).

The §102 rejection of claims 1-2 still applies. However, in the event that applicants re-instate the previous exclusion, claims 1-2 will then be rejected under §103 (only).

As indicated previously, Kitakabake discloses the following compound:

cyclo-Val-Val-Phe-Phe.

The reference does not disclose any of the following:

cyclo-Leu-Val-Phe-Phe.

cyclo-Val-Leu-Phe-Phe.

cyclo-Ile-Val-Phe-Phe.

cyclo-Val-Ile-Phe-Phe

Applicants have argued that the reference provides no motivation to modify the structure of the cyclopeptides. However, the question is not whether the peptide biochemist of ordinary skill would have expected better "gushing" effect in beer, but rather, whether the the peptide biochemist of ordinary skill would have expected substantially the same "gushing" effect in beer. The assertion is that the peptide biochemist of ordinary skill would have expected substantially the same gushing effect. Note that, in order for this rejection to be valid, there is not need to ascribe to the biochemist of ordinary skill any opinion one way or another about the effect of any peptide on NK-2 receptors. Applicants have framed the issue by arguing that the biochemist of ordinary skill would have to have an opinion about the effect of the disclosed peptide on NK-2 receptors. However, this is not true; the issue is whether the peptide biochemist of ordinary skill

would have expected that the "gushing" effect in beer would be largely undiminished by the modification.

The rejection is maintained.

*

It is suggested that applicants cancel claim 4. Alternatively claim 4 should be amended as deemed appropriate. Currently, the following is present in claim 4:

"[compounds] are made to react as shown in the diagram".

This phrase will have to be deleted, and replaced with something more specific. In addition, claim 4 should recite a step for isolation of the final product.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton. Phone: (703) 308-3213.

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600